26. (Amended) A method of Claim 23 wherein the tumor necrosis factor alpha antagonist is a receptor molecule which binds to tumor necrosis factor alpha.

27. (Amended) A method of Claim 26 wherein the receptor molecule is a tumor necrosis factor alpha receptor/immunoglobulin G fusion protein.

28. (Amended) A method of Claim 23 wherein the tumor necrosis factor alpha antagonist prevents or inhibits tumor necrosis factor alpha synthesis, tumor necrosis factor alpha release or its action on target cells.

29. (Amended) A method of Claim 28 wherein the tumor necrosis factor alpha antagonist is a phosphodiesterase inhibitor.

REMARKS

The above amendments to the specification are made to correct obvious typographical errors. The amendments to the claims are made to avoid certain issues raised by the Examiner under 35 U.S.C. § 112 and to clarify that which Applicants regard to be the invention. The amendments do not introduce new matter. The Office action will now be addressed under separate headings.

Applicants' Claim for Priority

The Examiner states that priority applications USSN 08/403,785 (filed October 6, 1993) and PCT/GB94/00462 (filed March 10, 1994) do not "support" the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "preventing Crohn's disease" and "tumor necrosis factor-mediated disease", as well as specific species of TNF antagonists. Applicants respectfully disagree with regard to the amended claims. As amended, many of the original and amended claims are entitled to an earlier effective filing date, as will

be explained below. With regard to the remaining claims, the subject matter recited therein is believed to be separately patentable over the prior art.

It is noted that parent application U.S. Serial No. 08/403,785 (hereinafter the "'785 application") is the U.S. National phase application of PCT/GB93/02070 (filed October 6, 1993) and U.S. Serial No. 08/617,737 (hereinafter the "'737 application") is the U.S. National phase application of PCT/GB94/00462 (filed March 10, 1994). As the Examiner discusses only the claim for priority with regard to these specific patent applications, the discussion will be limited to these applications. It is noted, however, that the present application additionally claims priority to USSN 07/958,248, filed October 8, 1992.

The '785 application, at page 4, lines 26-31, describes the treatment of autoimmune disease and inflammatory disease (such as rheumatoid arthritis) with anti-CD4 antibodies and anti-TNF antibodies. At page 11, line 22 to page 12, line 9, the application describes autoimmune and acute and chronic inflammatory diseases, specifically listing Crohn's disease and rheumatoid arthritis.

At page 5, lines 6-10, and page 10, lines 15-21, the application describes the use of other agents which affect the activation or interaction of CD4+ cells with antigen presenting cells and inflammatory mediators. At page 10, lines 12 and 31, the application specifically recites the use of cyclosporin in conjunction with the anti-TNF antibody. Specific TNF antagonists described in the parent application include pentoxyfilline (a phosphodiesterase inhibitor which is implicated in TNF synthesis (see page 11, lines 9-10)) and thalidomide (described at page 11, lines 10-11). TNF receptor immunoglobulin G fusion proteins are described, specifically, at page 11, line 8.

Thus, the parent specification provides a written description of the subject matter of the claims with, in many instances, literal support. It is noted that a literal

recitation of the claims is not required to provide support for a claim. As the Examiner has not provided any specific discussion of that which is present in the parent applications, vis-a-vis the present claims, it is believed that no further discussion of the description requirement referred to by the Examiner is necessitated here.

The Examiner states that the parent applications must also provide an enabling disclosure for the subject matter of the present claims. The Examiner does not state at this section of the action any reasons set forth to explain precisely why the parent specification lacks an enabling disclosure. It is believed that the grounds are the same as those set forth in questioning the enabling disclosure of the present specification. Thus, for the reasons discussed below relating to the enablement of the present specification, the parent specifications are also enabling for the claimed subject matter.

The Examiner has requested a copy of one of the parent PCT applications. As explained above, both PCT applications are pending before the USPTO as U.S. National phase applications. Applicants respectfully request that the Examiner consider the entire applications presented therein, which would include the present claims and the file history.

The Information Disclosure Statement

It is noted with appreciation that the Examiner has stated that the Information Disclosure Statement (IDS) from the continuation-in-part application (CIP) filed (August 1, 1997) has been considered in this application. Applicants filed an IDS on June 10, 1996 which is substantially duplicative with the IDS filed in the CIP. A copy is enclosed for the Examiner's records.

Drawings

Applicants acknowledge that the drawings submitted with the subject application were declared informal. Formal drawings will be filed no later than in response to the Notice of Allowance.

It is noted that the action does not appear to require submission of formal drawings at this time.

Correction of Typographical Errors and the Recitation of Trademarks

The specification has been amended to correct spelling and trademark errors.

Objection to the Specification and Rejection of Claims 1-45 Under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 1-45 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to use the invention. The Examiner states that it would require undue experimentation to practice the claimed methods and compositions with a reasonable expectation of success because of (1) the lack of predictability of the art; (2) the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions; (3) the absence of a specific and detailed description in the specification of how to effectively practice the claimed invention; and (4) the absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any TNF-mediated disease and preventing TNF-mediated disease with any TNF-specific antibody. Applicants respectfully disagree with this assessment.

To be enabling under 35 U.S.C. § 112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Court of Appeals for the Federal Circuit has stated that "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." Id.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. Id.

The specification teaches that TNF-mediated diseases can be treated in an individual by co-administering a CD4+ T cell inhibiting agent and a TNF antagonist to the individual in therapeutically effective amounts. Examples of the TNF-mediated diseases that can be treated are disclosed in the specification, for example, at pages 11-14. Examples of TNF antagonists that can be used in the claimed invention are provided in the specification, for example, at pages 15-37. Examples of CD4+ T cell inhibiting agents are disclosed in the specification, for example, at pages 37-40. Guidelines for route of administration and dosages are provided in the specification, for example, at pages 40-44.

Applicants have exemplified the claimed methods using monoclonal anti-TNFα and anti-CD4 antibodies in murine models for arthritis (see specification, e.g., pages 45-54). Examples 2 and 3 provide a comparison of other TNF antagonists with anti-CD4 antibodies (see pages 54-65). Example 4 establishes the therapeutic effect of anti-TNFα antibodies in conjunction with cyclosporine. Since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNFα), it is expected, based upon scientific reasoning, that the claimed methods work in the same manner using other anti-TNFα antibodies as well as other TNFα antagonists. This expectation is supported by the data presented in the specification. It is also expected, based upon scientific reasoning, that the claimed methods work in the same manner for other autoimmune and inflammatory diseases, known to be mediated by TNFα.

Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to use the claimed invention without undue experimentation. It is noted that Claims 15-22 claim methods of treating rheumatoid arthritis. Claims 23-30 relate to methods of treating Crohn's disease. Several of the dependent claims further define the active ingredient(s) to those for which *in vivo* data has been provided.

The Examiner states that:

> In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the clinical treatment of rheumatoid arthritis with multiple infusions with the anti-TNF antibody cA2 and methotrexate . . . accurately reflects the relative efficacy of any anti-TNF antibody or anti-TNF specificity as well as targeting any TNF-mediated diseases encompassed by the claimed methods and compositions.

Again, Applicants disagree with the conclusion. The Examiner has not provided the documentation apparently relied upon for this broad assertion. As such, it is difficult to rebut the particulars the Examiner is considering in support of this conclusion. In any event, the CIP application filed claiming priority to the present specification provides clinical data of the co-administration of the example recited in the rejection (methotrexate and anti-TNFα antibody, cA2). Thus, the argument has been rebutted with evidence, validating the teachings of the specification and establishing that coadministration of the two drugs is useful and that the result is dramatic.

Furthermore, the use of anti-TNFα antibodies in treating rheumatoid arthritis and Crohn's disease has been further supported by clinical data, as established by the enclosed U.S. patent (U.S. Patent No. 5,656,272; attached as Exhibit 1). There is no scientific reasoning provided by the Examiner which would suggest that the invention would not work with other members of the genus. Indeed, many of the remaining active agents described

in the specification have also been used in clinical trials, as evidenced by the prior art cited in the rejection down below. Thus, the Examiner's arguments have been rebutted.

The Examiner also states that:

> Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect . . .; (2) the protein may not reach the target area . . .; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use. . . . See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat. App. & Inter. 1992).

Again, however, the active ingredients employed in the claimed therapy are known for the treatment of these diseases individually. As established by the references of record, anti-TNFα antibodies, for example, have been successfully administered to patients. Certainly, the cited case law does not stand for the proposition that an applicant for patent must provide clinical studies for more than one species of a claimed genus. These vague and general possibilities of the fate of a therapeutic protein have been rebutted by evidence. No more should be required.

The Examiner goes on to state in the rejection that:

> Although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions than experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are

> treated generally after the inset of disease and not prior to disease.

These possibilities of difficulties which may be encountered in therapy have been rebutted by clinical evidence in patients after onset of chronic disease. Respectfully, many of the assertions presented in this argument are untrue. The argument as a whole does not consider the facts or evidence of the present application as well as the evidence presented by the references of record. Again, the argument does not relate to many of the dependent and specific claims.

The Examiner also states that:

> There is insufficient information or guidance as to how to select those patients to "prevent" the onset of the various diseases encompassed by the claimed invention. There is insufficient information to determine which markers would be predictive of said diseases in order to treat patients prior to the onset of said diseases, as a preventive regimen.

Applicants respectfully disagree. However, in an effort to advance prosecution of the subject application, the claims have been amended to recite the treatment of disease.

The Examiner refers to an article authored by inventors of the present invention. It is agreed that Elliott *et al.* (*Arth. Rheum.*, *36*(12):1681-1690 (1993)) disclose that the best specificity for treating arthritis is TNFα, rather than TNFβ. Thus, to eliminate issues in the present application, the claims have been amended to indicate that TNFα is the TNF specificity which is targeted.

Natanson *et al.* (*Ann. Int. Med.*, *120*(9):771-783 (1994)) is cited as teaching that murine anti-TNF antibodies have not been beneficial in treating sepsis and septic shock and that targeting TNF may be harmful. It is believed that, with regard to the claims, as amended, the issue is avoided.

The Examiner states that "there is insufficient guidance and direction as to the selection and enablement of any TNF

antagonist." Applicants respectfully disagree with this assessment.

As defined in the specification, TNF antagonists decrease, block, inhibit, abrogate or interfere with TNF activity *in vivo*. As set forth above, the specification provides a definition for the term. Applicants disclose that such TNF antagonists include anti-TNF antibodies and receptor molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signalling. Specific examples are provided as well. As the Examiner is undoubtedly aware, there are numerous TNF antagonists which are known in the art. Also as discussed above, working examples are also provided establishing efficacy in an animal model with a variety of distinct TNF antagonists. Since antibodies generally function by antagonizing or inhibiting the activity of its cognate antigen, it is expected, based upon scientific reasoning, that other agents which antagonize TNF can also be employed in the present invention. This conclusion is supported by data.

The Examiner goes on to state that:

> it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation. Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

Again, the scientific basis for the Examiner's conclusions have not been provided. In any event, the rejection is moot as it relates to the present claims.

It is noted that the Examiner appears only to consider the invention as it relates to the administration of a TNF antagonist and methotrexate. Please note that none of the claims pending in this application relate specifically to the administration of methotrexate.

In view of the foregoing discussion, withdrawal of the objection to the specification and rejection of Claims 1-45 under 35 U.S.C. § 112, first paragraph, is respectfully requested. Furthermore, in the event that the Examiner maintains one or more of the objections raised in the Office action, it is respectfully requested that each individual claim presented be considered separately.

Rejection of Claims 1-5, 8, 10, 14, 16, 20, 23, 24, 26, 28, 29, 31-32, 35, 40 and 43 Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 1-5, 10, 14, 20, 23, 26, 28, 31-32, 35, 40, and 43 (the reference to Claims 3, 8, 16, 24, 29 and 31 is believed to be a typographical error) have been rejected under 35 U.S.C. § 112, first and second paragraphs, for failing to describe the claimed invention in such full, clear, concise and exact terms as to enable the skilled artisan to make and use the claimed invention, and/or for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, first and second paragraphs.

As amended, the claims indicated include the following changes, made in response to specific rejections made by the Examiner:

A) Claims 1-3 and 14 are objected to as indefinite in the recitation of "tumor necrosis factor-mediated disease" because it

is not clear "whether said diseases reads on any inflammatory condition wherein TNF is present, wherein TNF has a direct role in pathology or wherein TNF has an indirect role in pathology." The Examiner states that "[a]lthough TNF contributes to certain conditions associated with inflammatory diseases, an artisan would not necessarily classify these diseases as TNF-mediated diseases, but rather inflammatory diseases wherein TNF plays some role." The rejection is not understood. The originally presented claims embrace the treatment of diseases that are mediated by TNF. The fact that there may exist other diseases where TNF is present but not TNF-mediated is not relevant to the issue. The originally presented claims did not embrace the treatment of such diseases.

Claims 1-3 and 14 are also objected to as ambiguous "in the recitation of TNF since there are different members associated with TNF, and it is not clear whether any disease with any role played by any TNF falls into the metes and bounds of TNF-mediated disease." Claims 1-3 and 14 have been cancelled in an effort to advance prosecution.

B) Claims 1-5, 10, 14, 20, 23, 26, 28, 31, 32, 35, 40 and 43 are objected to as indefinite in the recitation of "TNF antagonist" and "a receptor molecule which binds to tumor necrosis factor" "because their characteristics are not known." The Examiner states that the language "encompasses potentially thousands of different antagonists and it is not apparent from the disclosure which particular antagonists or receptor molecules are being referred to." Applicants respectfully disagree with this assessment, as it pertains to the pending claims.

As defined in the specification, the term "TNF antagonist" refers to an antagonist that decreases, blocks, inhibits, abrogates or interferes with TNF activity *in vivo* (see, e.g., page 15, lines 15-17). Thus, a clear definition that would be readily understood by the skilled artisan has been provided in the specification. Applicants disclose that TNF antagonists

include anti-TNF antibodies and receptor molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signalling (see specification, e.g., page 125 lines 17-33). Thus, the specification provides many examples of what is envisioned by the term.

As defined in the specification, the term "receptor molecule which binds to tumor necrosis factor" refers to a soluble TNF receptor (see specification, e.g., page 35, line 7) that binds TNF with high affinity and low immunogenicity (see specification, e.g., page 35, lines 7-13). Thus, a clear definition that would be readily understood by the skilled artisan has been provided in the specification. Applicants disclose that receptor molecules which bind to tumor necrosis factor include the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors, TNF multimeric molecules and TNF immunoreceptor fusion molecules (see specification, e.g., page 35, line 13 - page 37, line 37). Thus, the specification provides many examples of what is envisioned by the term.

Thus, it is respectfully submitted that the terms "TNF antagonist" and "receptor molecule which binds to tumor necrosis factor" are definite. The fact that the terms may be considered by the Examiner to be "broad" or the fact that they potentially embrace "thousands" of compounds certainly does not support the argument that the claims are either vague or indefinite. See M.P.E.P. § 2173.04, "Breadth Is Not Indefiniteness."

The Examiner also states that:

> There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "antagonists" nor is there evidence provided that such "antagonists" would be effective in inhibiting TNF either in vitro or in vivo . . . . It would require undue experimentation to produce all such possible antagonists without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such antagonists. It appears that undue experimentation would be required of one skilled

in the art to practice the claimed method using the teaching of the specification alone.

Applicants respectfully disagree for the reasons set forth above. Briefly, compounds within this class are known for use in the treatment of disease. Nothing more is required.

Rejection of Claims 1-45 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-45 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that Claims 1-45 are indefinite in the recitation of "tumor necrosis factor" because "there are different members of this genus and it is not clear which TNF is intended."

The claims have been amended to recite "tumor necrosis factor alpha." Support for this amendment is found in the specification, for example, at page 5, lines 5-13; page 15, line 14 - page 18, line 6; page 20, line 19 - page 21, line 24; page 35, line 6 - page 36, line 33; and page 45, line 1 - page 76, line 24. Support for this amendment is also found in the priority documents listed in the specification at page 1, lines 4-12.

As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-4, 6, 8, 10, 14-16, 20, 40-41 and 43 Under 35 U.S.C. § 102(a) & (b)

Claims 1-4, 6, 8, 10, 14-16, 20, 40-41 and 43 have been rejected under 35 U.S.C. § 102(a) & (b) as being anticipated by Williams *et al.* (*Proc. Natl. Acad. Sci. USA, 91*:2762-2766 (1994)).

Williams *et al.* (coauthored by the inventors of the subject application) is cited by the Examiner as exemplifying the use of

anti-CD4 and anti-TNF antibodies in the amelioration of established arthritis. This reference was published in 1994, prior to the effective filing date of this application, as discussed above. As such, it is not prior art against the claims.

Withdrawal of this rejection under 35 U.S.C. § 102 is respectfully requested.

Rejection of Claims 1-45 Under 35 U.S.C. § 103

Claims 1-45 have been rejected under 35 U.S.C. § 103 as being unpatentable over Williams *et al.*, Steinman *et al.*, Bender *et al.* and Celltech (WO92/07585) in view of Elliott *et al.* (*Arth. Rheum.*, *36*(12):1681-1690 (1993); hereinafter "Elliott I"), Elliott *et al.* (*Lancet*, *344*:1105-1110 (1994); hereinafter "Elliott II"), Flesch *et al.* (*Blood*, *79*(12):3362-3368 (1992); hereinafter "Herve *et al.*", after the first named author), Kay *et al.*, Brahn *et al.*, Markowitz*et al.*, Thorbecke *et al.*, Piguet *et al.* and Heinemann *et al.* or Bianco *et al.*

Applicants' claimed invention relates to methods of treating a tumor rheumatoid arthritis and Crohn's disease in an individual comprising co-administering a CD4+ T cell inhibiting agent and a TNFα antagonist to the individual.

Teachings of the Cited References

Williams *et al.*

As discussed above, Williams *et al.* is not prior art against the claims.

Steinman *et al.*

Steinman *et al.* teach a method of treating a patient for an autoimmune disease that is mediated by Leu3 phenotype T cells (e.g., rheumatoid arthritis) comprising administering an anti-CD4 antibody to the patient. Steinman *et al.* state that the anti-CD4 antibody can be co-administered with antibodies that are directed

to other medical conditions, such as cancer (Steinman *et al.*, col. 2, l. 50-53). Compare, with the teachings of Lorenz *et al.*, *Rheumatology in Europe, 24*(3):99-106 (1995); copy attached as Exhibit 2. Steinman *et al.* do not teach or suggest that the anti-CD4 antibody can be co-administered with antibodies that are directed to the same medical condition, that is, to autoimmune disease. In particular, Steinman *et al.* do not teach or suggest treating a patient for an autoimmune disease (or other TNFα-mediated disease) by co-administering an anti-CD4 antibody (or other CD4+ T cell inhibiting agent) and an anti-TNFα antibody (or another TNFα antagonist) to the patient. Steinman *et al.* also do not teach or suggest a composition comprising a CD4+ T cell inhibiting agent and a TNFα antagonist. Steinman *et al.* do not even mention TNFα antagonists.

Bender *et al.*

Bender *et al.* teach the use of a TNF production-inhibiting compound of Formula II (disclosed in the reference) for treatment or prophylaxis of a disease state in a human which is exacerbated or caused by excessive or unregulated TNF production (e.g., rheumatoid arthritis and inflammatory bowel disease) (Bender *et al.*, col. 21, l. 31-53; and col. 22, l. 60-65).

Bender *et al.* also teach the use of an IL-1 production inhibiting compound of Formula I (disclosed in the reference) for treatment or prophylaxis of a disease state in a human which is exacerbated or caused by excessive or unregulated IL-1 production (e.g., rheumatoid arthritis and inflammatory bowel disease) (Bender *et al.*, col. 18, l. 45-48; and col. 18, l. 56-57).

Bender *et al.* do not teach or suggest treating rheumatoid arthritis or inflammatory bowel disease in an individual by co-administering a CD4+ T cell inhibiting agent and a TNFα antagonist to the individual. Bender *et al.* also do not teach or suggest a composition comprising a CD4+ T cell inhibiting agent and a TNFα antagonist. Bender *et al.* do not even mention CD4+ T cell inhibiting agents or TNFα antagonists.

Celltech

The Celltech reference teaches the use of an anti-TNF antibody in combination with a xanthine derivative (e.g., pentoxifylline) in treatment of disorders associated with elevated levels of TNFα (e.g., autoimmune disease, rheumatoid arthritis, AIDS) (Celltech, e.g., Abstract; page 1, lines 3-6; page 2, lines 16-21; and page 9, line 18 - page 10, line 11). The Celltech reference also teaches compositions comprising an anti-TNF antibody and a xanthine derivative.

The Celltech reference does not teach or suggest treating a TNFα-mediated disease in an individual by co-administering a CD4+ inhibiting agent and an anti-TNFα antibody, a xanthine derivative or other TNFα antagonist, to the individual. The Celltech reference also does not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Elliott I and Elliott II

Elliott I and Elliott II (coauthored by the inventors of the subject application) teach the use of chimeric monoclonal antibody cA2 in the treatment of patients with active rheumatoid arthritis.

Neither Elliott reference teaches or suggests treating rheumatoid arthritis (or other TNFα-mediated disease) in an individual by co-administering a CD4+ inhibiting agent and an anti-TNFα antibody (or other TNFα antagonist) to the individual. The cited Elliott references also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist. The Elliott references do not mention CD4+ inhibiting agents.

Herve *et al.*

Herve *et al.* report the results of a phase I-II multicenter pilot study assessing the clinical efficacy of a monoclonal anti-TNFα antibody (B-C7) in the treatment of patients with refractory severe acute graft-versus-host disease (aGVHD). The reference

does not teach or suggest the co-administration of a CD4+ inhibiting agent and a TNFα antagonist in the treatment of rheumatoid arthritis or Crohn's disease.

Kay *et al.*

Kay *et al.* teach the use of cyclosporin A (or other immunosuppressant with the same or a similar mode of action) for the treatment of diseases characterized by airflow obstruction or chronic sinusitis (Kay *et al.*, e.g., page 11, line 25 - page 12, line 9; page 15, lines 12-17). Suitable other immunosuppressants disclosed by Kay *et al.* include FK506, rapamycin and anti-CD4 antibodies (Kay *et al.*, e.g., page 17, lines 12-19). Thus, Kay *et al.* teach the use of cyclosporin, FK506, rapamycin or an anti-CD4 antibody for the treatment of diseases characterized by airflow obstruction or chronic sinusitis. The abstract teachings list a genus of cyclosporin and immunosuppressants which are to be administered in the alternative. This interpretation is made clear from a reading of the entire publication.

Thus, contrary to the Examiner's assertion, Kay *et al.* do not teach or suggest the use of anti-CD4 antibodies in conjunction with immunosuppressants such as cyclosporin as an anti-inflammatory regimen. That is, Kay *et al.* do not teach or suggest a combination therapy for treatment of diseases characterized by airflow obstruction or chronic sinusitis. Thus, contrary to the Examiner's contention, Kay *et al.* do not provide "an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition".

Furthermore, Kay *et al.* do not teach or suggest treating broadly TNFα-mediated diseases or inflammatory diseases in an individual, much less by co-administering a CD4+ inhibiting agent and a TNFα antagonist to the individual. The teachings of Kay *et al.* are limited to the treatment of lung or bronchial disease with a specific class of compounds. Kay *et al.* also do not teach

or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Markowitz *et al.*

Markowitz *et al.* disclose the use of cyclosporin in the treatment of inflammatory bowel disease (Markowitz *et al.*, pages 418-419).

Markowitz *et al.* are also cited by the Examiner as teaching at page 413 targeting TNF in the treatment of inflammatory bowel disease. This is not understood. At page 413, Markowitz *et al.* state that "TNF appears to be a proximal mediator of inflammation and shock." This, however, does not teach or suggest targeting TNF in the treatment of inflammatory disease. It certainly does not teach or suggest treating inflammatory bowel disease (or other TNFα-mediated disease) in an individual by co-administering cyclosporin (or other CD4+ inhibiting agent) and a TNFα antagonist to the individual. Markowitz *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Brahn *et al.*

Brahn *et al.* disclose in their abstract the results from a study on the effects of TNFα, methotrexate, or combination cyclosporine and methotrexate therapy on collagen arthritis. They report that (1) TNFα therapy is "not therapeutically beneficial and may actually exacerbate collagen arthritis"; (2) methotrexate therapy is ineffectual at treating collagen arthritis; and (3) combination cyclosporine and methotrexate therapy attenuates the disease.

Brahn *et al.* do not teach or suggest treating arthritis (or other TNFα-mediated disease) in an animal by co-administering a CD4+ inhibiting agent and a TNFα antagonist to the animal. Brahn *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist. In fact, Brahn *et al.* would appear to teach away from the claimed invention.

Thorbecke *et al.*

Thorbecke *et al.* examine the role of endogenously produced TGFβ and TNFα in the pathogenesis of collagen type II-induced arthritis (CIA) in DBA/1 mice by determining the effect of neutralizing monoclonal antibodies to these factors on the course of the disease. Thorbecke *et al.* found that endogenously produced as well as systemically administered TGFβ_1 and TNFα had opposite effects. Specifically, Thorbecke *et al.* found that TGFβ_1 and anti-TNFα protected against CIA, whereas anti-TGFβ_1 and TNFα increased CIA incidence and/or severity.

Contrary to the Examiner's statement, Thorbecke *et al.* do not teach or suggest the use of soluble TNF receptors in the treatment or arthritis. Thorbecke *et al.* also do not teach or suggest treating arthritis (or other TNFα-mediated disease) in an animal by co-administering a CD4+ inhibiting agent and a TNFα antagonist to the animal. Thorbecke *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Piguet *et al.*

Piguet *et al.* teach that the long-term evolution of collagen arthritis in mice can be prevented with administration of an anti-TNFα antibody or a soluble TNF receptor to the mice at an early phase of the disease.

Piguet *et al.* do not teach or suggest treating arthritis (or other TNFα-mediated disease) in an animal by co-administering a CD4+ inhibiting agent and a TNFα antagonist to the animal. Piguet *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Heinemann *et al.*

Heinemann *et al.* teach the use of 1,2,4-dithiazolium salts of Formula I (disclosed in the reference) as TNF inhibitors. Heinemann *et al.* also report the use of pentoxifylline and

thalidomide for blocking of TNF synthesis or TNFα receptor binding (Heinemann *et al.*, col. 2, l. 35-41).

Heinemann *et al.* do not teach or suggest treating a TNFα-mediated disease in an individual by co-administering a CD4+ inhibiting agent and a TNFα antagonist to the individual. Heinemann *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Bianco *et al.*

Bianco *et al.* teach the use of xanthine derivatives (e.g., pentoxifylline) for treatment of a variety of diseases, including autoimmune disease, HIV infection, rheumatoid arthritis, Crohn's disease and graft versus host disease (Bianco *et al.*, e.g., col. 3, l. 6-49; col. 8, l. 18 - col. 11, l. 11).

Bianco *et al.* do not teach or suggest co-administering a CD4+ inhibiting agent and a TNFα antagonist to treat a TNFα-mediated disease. Bianco *et al.* also do not teach or suggest a composition comprising a CD4+ inhibiting agent and a TNFα antagonist.

Summary of the References

In summary, the Examiner has cited 13 references which relate to the administration of various active ingredients in the treatment of various disease states. Many of the references are not believed to be relevant to the remaining pending claims, directed to the treatment of rheumatoid arthritis or Crohn's disease. At best, the remaining references describe the administration of either a CD4+ antagonist or a TNF antagonist. None of the references teach or suggest the co-administration of a CD4+ antagonist and a TNF antagonist to treat rheumatoid arthritis and Crohn's disease.

The Combination of References

In support of the rejection, the Examiner states:

> [T]he prior art taught all of the claimed TNF antagonists as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said TNF antagonists to achieve the same desired diminished TNF activity to suit the nature of the therapeutic regimen.
>
> One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as cyclosporin and xanthine derivatives. Combination therapies were well known in the art and cyclosporin, xanthine derivatives and anti-inflammatory agent such as TNF-receptors and anti-TNF antibodies were shown to be effective in vivo.

The actual basis or support for the assertion made or conclusion drawn in the first paragraph is not provided. It is not seen that the cited references do, in fact, teach "all of the claimed TNF antagonists as well as their combinations." This is simply not believed to be true or even relevant to the issue of the claimed invention. Furthermore, Applicants respectfully disagree with the Examiner's conclusion in the second paragraph that the claimed invention was obvious.

Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion

and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

None of the cited references, nor their combination, teach or suggest co-administration of a CD4+ T cell inhibiting agent and a TNFα antagonist to a mammal for treating rheumatoid arthritis, Crohn's disease, acute or chronic immune disease associated with a transplantation, or other TNFα-mediated disease. None of the cited references, nor their combination, teach or suggest compositions comprising a CD4+ T cell inhibiting agent and a TNFα antagonist.

In addition, one of ordinary skill in the art would not have been able to predict, given the cited references, whether co-administration of a CD4+ T cell inhibiting agent and a TNFα antagonist to a mammal would be highly effective in methods for treating rheumatoid arthritis or Crohn's disease. That is, none of the cited references, nor their combination, teach the effective treatment of a mammal with an rheumatoid arthritis or Crohn's disease by co-administration of a CD4+ T cell inhibiting agent and a TNFα antagonist.

The Examiner goes on to state in the rejection that:

> It was prima facie obvious to combine two compositions each of which is taught by [the] prior art to be useful for [the] same purpose in order to form a third composition that is to be used for [the] very same purpose; [the] idea of combining them flows logically from their having been individually taught in [the] prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

It is not seen that the cited case provides a *per se* rule that any combination therapy is obvious where the individual components have been suggested as useful individually.

In any event, Applicants demonstrated the unexpected result that combination therapy with a CD4+ T cell inhibiting agent and a TNFα antagonist produced a significantly improved response compared to that obtained with each agent alone. For example, Example 1 shows significant therapeutic improvement using combination therapy with anti-TNFα and anti-CD4 antibodies in

murine models for arthritis in comparison to the results obtained with each agent alone (see specification, e.g., Figure 1 and Tables 1-4). Indeed, significant improvement of the combination therapy was observed even in comparison to where optimal dosages of each antibody (anti-TNFα antibody or anti-CD4 antibody) were administered alone. Examples 2 and 3 show that combination therapy with a TNFα receptor/IgG fusion protein and anti-CD4 antibody in murine models for arthritis produced markedly superior results than the results obtained with each agent alone (see specification, e.g., Tables 7-9 and Figure 3). Examples 4-6 illustrate the therapeutic effect of combination therapy with anti-TNFα antibodies and cyclosporine. The data show a significant ameliorative effect between cyclosporin and anti-TNFα antibody (see specification, e.g., Figure 4-7 and Tables 10-13). The magnitude of these results in the treatment of arthritis could not have been reasonably predicted from the cited references. There is nothing of record which would indicate that those of ordinary skill in the art would reasonably conclude that a dramatic improvement would be expected by combination therapy with a CD4+ T cell inhibiting agent and an anti-TNFα antibody.

Significant improvement of the combination therapy was observed even in comparison to where optimal dosages of anti-TNFα antibody were administered alone. It is by now well settled that significant improvements in combination therapies can rebut a *prima facie* case of obviousness. See In re Kollman, 201 U.S.P.Q. 193 (C.C.P.A. 1979). See also MPEP § 716.02(a).

The Examiner does not appear to consider the data presented in the specification at all in the rejection of the present claims.

In summary, the cited references, either alone or in combination, do not teach or suggest the claimed invention (methods of treating rheumatoid arthritis and Crohn's disease in a mammal comprising co-administering a CD4+ T cell inhibiting agent and a TNFα antagonist). The cited references, either alone or in combination, do not provide a reasonable expectation that

co-administration of a CD4+ T cell inhibiting agent and a TNFα antagonist to a mammal would be effective in methods for treating a TNFα-mediated disease. The cited references, either alone or in combination, also do not reasonably suggest that the unexpected and superior results achieved and described in the subject application were possible. Thus, withdrawal and reconsideration of this rejection under 35 U.S.C. § 103 are respectfully requested.

Rejection of Claims 1-45 Under the Doctrine of Obviousness-Type Double Patenting

Claims 1-45 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 43-57 of copending application U.S. Serial No. 08/403,785.

Applicants intend to file a terminal disclaimer upon resolution of the remaining issues. It is noted that this is a provisional rejection as neither application has been allowed or patented.

Common Ownership

The Examiner states that commonly assigned U.S. Serial No. 08/403,785 would form the basis for a rejection of Claims 1-45 under 35 U.S.C. § 103:

> if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made.

The Examiner further states that:

> the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter.

Applicants respectfully traverse this requirement.

It is noted that 37 C.F.R. § 1.78(c) is applicable only to commonly owned cases naming different inventors. See 37 C.F.R. § 1.78(c). The inventors of the subject application and of U.S. Serial No. 08/403,785 are the same. That is, the inventors of the claimed subject matter in both applications are Marc Feldmann, Ravinder N. Maini and Richard O. Williams. Therefore, the requirement of 37 C.F.R. § 1.78(c) is not applicable to the subject application. See also MPEP § 804.03.

Thus, withdrawal of this requirement 37 C.F.R. § 1.78(c) is respectfully requested.

Provisional Rejection of Claims 1-45 under 35 U.S.C. § 103

Claims 1-45 have been provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application U.S. Serial No. 08/403,785 (hereinafter the "'785 application") in view of other known inhibitors used in the treatment of inflammation, including immunosuppresive agents such as cyclosporin or xanthine derivatives such as pentoxifylline in the treatment of TNFα-mediated inflammation. It is noted that the paragraph of 35 U.S.C. § 102 relied upon by the Examiner in rejecting the claims is not set forth. As such, it is difficult to reply fully.

The subject application is CIP of PCT/GB94/00462 (filed March 10, 1994), which is a CIP of the '785 application, which is the U.S. National phase application of PCT/GB93/02070 (filed October 6, 1993). Applicants' are entitled to the effective filing date of the '785 application, for the reasons set forth above. As such, the '785 application is not prior art against the claims.

Furthermore, any patent which may issue from the parent application enjoys the same inventive entity as the subject application and is not, accordingly, by "another" and is not prior art under 35 U.S.C. § 102 (e), (f) or (g).

Withdrawal of this provisional rejection under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

It is respectfully submitted that the claims are in condition for allowance. The Examiner is respectfully requested to reconsider the rejections and to withdraw them.

If the Examiner believes that a telephone conversation would be helpful in expediting the prosecution of this application, the Examiner is requested to call the undersigned at (617) 861-6240.

Respectfully submitted,

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